

Appln. No. 09/763,370  
Amd. dated January 15, 2004  
Reply to Office Action of July 15, 2003

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Canceled)

2. (previously presented) The method of claim 6, wherein the marker that reflects the activity of osteoblasts is:

(1) a marker associated with the phase of osteoblast proliferation and matrix formation and a marker associated with the phase of calcification; or

(2) a marker associated with the phase of matrix maturation and a marker associated with the phase of calcification.

3. (previously presented) The method according to claim 6, wherein the marker that reflects the activity of osteoblasts is:

(1) Carboxyterminal propeptide of type I procollagen or Amino terminal propeptide of type I procollagen and osteocalcin; or

(2) Bone specific alkaliphosphatase and osteocalcin.

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4. (previously presented) The method according to claim 6, wherein the marker that reflects the action of osteoclasts is a marker associated with bone type I collagen.

5. (previously presented) The method according to claim 6, wherein the marker that reflects the action of osteoclasts is deoxypyridinoline and/or Carboxyterminal telopeptide of type I collagen.

6. (Currently Amended) A method of diagnosing amelioration and/or exacerbation of metastasis of malignant tumor to bone in a patient with a cancer disease,  
\_\_\_\_\_ using two markers comprising both a first marker  
that reflects ~~reflect~~ the activity of osteoblasts and a second  
marker ~~markers~~ that reflects ~~reflect~~ the action of  
osteoclasts,

1) wherein the markers that reflect the activity of  
osteoblasts are

a) one or more markers associated with the  
phase of calcification, and

b) one or more markers associated with the  
phase of osteoblasts proliferation and/or matrix formation,

2) wherein the one or more markers that reflect the  
activity of osteoclasts are markers associated with

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osteoclasts targeted to evaluation of worsening of the disease,

wherein the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed by monitoring said ~~two~~ markers, 7 said ~~first~~ marker being associated with osteoblasts and ~~targeted to evaluation of therapeutic effect,~~ and said ~~second~~ marker being associated with osteoclasts and ~~targeted to evaluation of worsening of the disease.~~

7. (Canceled)

8. (currently amended) A method of evaluating the ~~therapeutic efficacy of a drug~~ drugs for treatment of a cancer disease,

using one or more a marker formative markers that reflects the activity of osteoblasts and ~~a marker that reflects the action~~ one or more resorptive markers that reflect the activity of osteoclasts,

1) wherein the markers that reflect the activity of osteoblasts are

a) one or more markers associated with the phase of calcification, and

b) one or more markers associated with the phase of osteoblasts proliferation and/or matrix formation,

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2) wherein the one or more markers that reflect the activity of osteoclasts are markers associated with osteoclasts targeted to evaluation of worsening of the disease.

whereby wherein the amelioration of bone metastasis or therapeutic effect and the degree of the exacerbation of bone metastasis are diagnosed correctly by monitoring said ~~two~~ markers, ~~one associated with osteoblasts and targeted to evaluation of therapeutic effect, and the other associated with osteoclasts and targeted to evaluation of worsening of the disease.~~

9. (currently amended) The method according to claim 8, wherein the drug evaluated is a cancer control therapeutic agent.

10. ((currently amended) The method according to claim 8, wherein the drug evaluated is a bone resorption suppressant.

11. ((currently amended) The method according to claim 8, wherein the drug evaluated is an endocrine therapeutic agent.

12. (Previously presented) The method according to

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claim 8, wherein the marker that reflects the activity of osteoblasts is:

(1) a marker associated with the phase of osteoblast proliferation and matrix formation and a marker associated with the phase of calcification; or

(2) a marker associated with the phase of matrix maturation and a marker associated with the phase of calcification.

13. (Previously presented) The method according to claim 8, wherein the marker that reflects the activity of osteoblasts is:

(1) Carboxyterminal propeptide of type I procollagen or Amino terminal propeptide of type I procollagen and osteocalcin; or

(2) Bone specific alkaliphosphatase and osteocalcin.

14. (Previously presented) The method according to claim 8, wherein the marker that reflects the action of osteoclasts is a marker associated with bone type I collagen.

15. (Previously presented) The method according to claim 8, wherein the marker that reflects the action of osteoclasts is deoxypyridinoline and/or Carboxyterminal telopeptide of type I collagen.

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16. (currently amended) The method according to claim 8, wherein there is used:

1) the ratio of A/B in which A is a marker associated with osteoblast calcification and B is a marker associated with osteoblast proliferation or a marker associated with matrix formation, and a marker associated with bone type I collagen, or

2) a ratio of A/B in which A is a marker associated with osteoblast calcification and B is the measured value of a marker associated with osteoblast matrix formation, and the measured value of a marker associated with bone type I collagen;

wherein the ratio of A/B is a Z value of an A to Z value of B in which said Z value is:

(an average of measured values for patients with bone metastasis)/(a standard deviation of a patient without bone metastasis).

17. (currently amended) The method according to claim 8, wherein there is used:

1) a ratio of A/B in which A is osteocalcin and B is Carboxyterminal propeptide of type I pro-collagen or Amino terminal propeptide of type I procollagen and Carboxyterminal telopeptide of type I collagen, or

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2) a ratio of A/B in which A is osteocalcin and B is Bone specific alkaliphosphatase and Carboxyterminal telopeptide of type I collagen;

wherein the ratio of A/B is a Z value of an A to Z value of B in which said Z value is:

(an average of measured values for patients with bone metastasis)/(a standard deviation of a patient without bone metastasis).

18. (Cancelled)

19. (canceled).

20. (currently amended) The method according to claim 6, wherein there is used:

1) a ratio of A/B in which A is a marker associated with osteoblast calcification and B is a marker associated with osteoblast proliferation of a marker associated with matrix formation, and a marker associated with bone type I collagen, or

2) a ratio of A/B in which A is a marker associated with osteoblast calcification and B is the measured value of a marker associated with osteoblast matrix formation, and the measured value of a marker associated with bone type I collagen;

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wherein the ratio of A/B is a Z value of an A to Z  
value of B in which said Z value is:

(an average of measured values for patients with  
bone metastasis) / (a standard deviation of a patient without  
bone metastasis).

21. (currently amended) The method according to  
claim 6, wherein there is used:

1) a ratio of A/B in which A is osteocalcin and B  
is carboxy-terminal propeptide of type I procollagen or amino-  
terminal propeptide of type I procollagen, and carboxy-  
terminal telopeptide of type I collagen, or

2) a ratio of A/B in which A is osteocalcin and B  
is bone-specific alkaline phosphatase, and carboxy-terminal  
telopeptide of type I collagen;

wherein the ratio of A/B is a Z value of an A to Z  
value of B in which said Z value is:

(an average of measured values for patients with  
bone metastasis) / (a standard deviation of a patient without  
bone metastasis).

22-24. (canceled)